



EBV相关性胃癌的流行病学、分子特征及其免疫治疗策略的临床应用

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摘要 EBV相关性胃癌(EBV-associated gastric cancer, EBVaGC)是一种与EB病毒(Epstein-Barr virus, EBV)相关的胃癌类型, 虽然其发病率较低, 但具有独特的临床特点. EBVaGC患者多为年轻男性, 且初诊时大多为局部晚期, 尽管如此, 其预后较好. 该类型胃癌的肿瘤微环境中常见显著的淋巴细胞浸润, 呈现出更“热”的免疫微环境. 研究表明, 晚期EBVaGC患者对免疫检查点抑制剂的治疗反应优于普通胃癌患者. 本文综述了EBVaGC的疾病特征、临床诊治进展及免疫治疗的潜力, 旨在为深入探讨该病的免疫微环境、免疫治疗策略及耐药机制提供指导, 为临床治疗与前瞻性试验设计提供理论依据, 以期推动该领域的进一步研究.

关键词 胃癌, EB病毒, 流行病学特征, 临床特征, 预后

EBV相关性胃癌(EBV-associated gastric cancer, EBVaGC)是一种与EB病毒(Epstein-Barr virus, EBV)相关的胃癌类型. 虽然EBV的致癌机制尚未完全明了, 但研究表明, EBV感染能促进胃癌细胞的增殖、侵袭和转移等恶性行为. 此外, EBV编码的基因产物也可能对胃癌细胞的生物学行为产生影响. 早在1990年, Burke等人^[1]首次确认了EBV在胃癌中的致病作用, 随后Shibata和Weiss^[2]证实了胃癌及异型增生细胞中存在EBV基因组. 2010年, TCGA(癌症基因组图谱)提出了胃癌的分子分型^[3], 将胃癌分为四个亚型: EB病毒感染型(EBV)、微卫星不稳定型(microsatellite instability, MSI)、基因组稳定型(genomically stable, GS)和染色体不稳定型(chromosomal instability, CIN), 其中EBV

亚型占比8.8%. 与EBV阴性胃癌(EBV negative gastric cancer, EBVnGC)相比, EBVaGC在临床特征、肿瘤微环境及预后方面具有独特性. EBVaGC通常表现为较热的肿瘤免疫微环境, 患者可能从免疫治疗中获益, 并且整体预后较好^[4,5].

1 EBV相关性胃癌的发病率和临床病理特征

1.1 EBV阳性胃癌的病理类型与组织学特征

EBV阳性胃癌(EBVaGC)从病理学上可分为几种亚型, 其中包括淋巴上皮瘤样癌(lymphoepithelioma-like carcinoma, LELC)、克罗恩样淋巴细胞反应样癌

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及其他传统的胃腺癌类型^[6]。在EBVaGC中, LELC是一种重要的组织学亚型, 具有显著的淋巴组织增生浸润, 且肿瘤细胞常被淋巴组织包围。这类肿瘤的形态学特征包括大量淋巴细胞浸润, 肿瘤细胞边界模糊, 肿瘤呈合胞式生长, 形成不规则且不成熟的腺体结构。此外, 黏膜病变部位的小腺管或索状结构呈现不规则分枝及愈合增生样变化, 即所谓的“花边样”改变。克罗恩样淋巴细胞反应样癌是EBVaGC中的另一重要亚型, 其镜下特征与克罗恩病的某些病理表现相似, 表现为淋巴细胞浸润, 尽管炎症程度较轻, 并且很少或没有结缔组织生成。除这两种亚型外, EBBaGC中也常见传统的胃腺癌, 其特点是癌细胞分化程度不一, 淋巴细胞浸润相对较少, 并伴有明显的结缔组织增生。

1.2 EBV阳性胃癌的分子标志物与诊断方法

EBER-ISH是诊断EBV阳性胃癌的金标准。研究人员发现, EBBaGC患者的肿瘤组织中可检测到*LMP1*和*LMP2A*的过表达^[7,8], 这两种跨膜蛋白均位于细胞质膜上, 作为持续激活的生长因子受体, 在EBV感染的B细胞中发挥关键作用。它们共同模拟正常抗原信号, 推动B细胞分化为记忆B细胞^[9,10]。

关于EBV-DNA拷贝数的研究在EBVaGC中较少, 但已有研究发现, EBV-DNA拷贝数的动态变化在鼻咽癌筛查、治疗效果评估及预后判断中具有重要价值。在EBVaGC中, 初诊时EBV-DNA拷贝数升高的比例并不高, 52.1%的EBVaGC患者的血浆EBV-DNA>0拷贝/mL, 当临界值为100拷贝数/mL时, EBBaGC的血浆EBV-DNA阳性率为43.6%。研究还发现, EBV-DNA拷贝数的升高与较差的预后相关, 同时其动态变化也能预测化疗效果, EBV-DNA拷贝数升高可能预示着肿瘤进展^[11]。一项来自伊朗的研究表明, EBV阳性胃癌患者的血浆EBV-DNA拷贝数显著高于EBV阴性胃癌患者^[12]。另一项研究采用PCR方法检测, 62.8%的EBVaGC患者外周血中可检测到EBV-DNA, 显著高于EBV阴性胃癌^[13]。因此, 建议对EBVaGC患者进行外周血EBV-DNA检测, 并根据基线EBV-DNA拷贝数的高低, 进行动态监测其变化, 以便及时评估疾病进展及治疗效果。

1.3 EBBaGC的临床特征与患者人群

文献报道, EBBaGC的发生率为1.3%~30.9%^[3,11,14,15],

在巴布亚新几内亚, EBBaGC的发生率为1.3%; 在美国胃癌患者中, 占比为16%; 而在文莱, 其发生率高达30.9%。在中国, EBBaGC在胃癌患者中的占比为5.1%~10.6%。中山大学肿瘤医院徐瑞华教授团队的研究发现, EBBaGC的发生率与胃癌的TNM分期相关, 在I~IV期胃癌患者中, EBBaGC的发生率分别为9.3%, 9.9%, 6.7%和1.4%^[11]。

EBVaGC发病较年轻, 患者的中位发病年龄为55岁, 明显低于普通胃癌患者; 且男性患者较多, EBBaGC的男女比例为9:1, 而普通胃癌为2:1。EBVaGC常见于近端胃, 包括贲门、胃底^[16]。初诊时III期患者比例高。一项回顾性研究中显示, EBBaGC患者中I~IV期的患者比例分别为19.3%, 19.3%, 50%和11.4%^[17]。根据TCGA的分型, EBBaGC和微卫星不稳定型(MSI-H)胃癌被视为独立的亚型^[18], 在另一项研究EBV胃癌免疫治疗的分析中也报道了EBV和微卫星稳定型(microsatellite stability, MSS)胃癌的关系, 发现25例EBV阳性胃癌都是MSS^[19]。然而, 研究人员在一项观察性研究中发现, 140例EBVaGC患者中有2例为MSI-H类型, 这表明EBVaGC和MSI-H胃癌患者并非互斥关系^[11]。考虑到EBV相关性胃癌和MSI-H在胃癌中的发生率均较低, 因此在样本量较小的研究中, 难以观察到两者同时阳性的病例。

2 EBBaGC的肿瘤微环境及免疫特征

2.1 EBBaGC的肿瘤微环境特点

EBVaGC存在显著的淋巴细胞浸润, 且可观察到三级淋巴结构^[20]。单细胞测序分析对比了EBV阳性和阴性胃癌患者治疗前胃镜活检组织的微环境特征, 结果发现, EBV阳性胃癌呈现免疫炎症型微环境, 表现为丰富的T细胞和B细胞浸润; 而EBV阴性胃癌则表现为“冷肿瘤”微环境, T细胞和B细胞浸润较少, 且免疫抑制性细胞(如髓系细胞)浸润较多^[21]。

2.2 EBBaGC的基因突变与分子特征

EBVaGC具有独立的肿瘤微环境(图1)。TCGA测序数据显示, EBBaGC有更高水平的*MHC-I*和*MHC-II*表达, 以CPG岛甲基化表型(CpG)为特征, 表现为*CDKN2A/p16INKA*启动子甲基化, 但缺乏*MLH1*高甲基化。*PIK3CA*与*ARID1A*存在高频突变, 而*TP53*突变

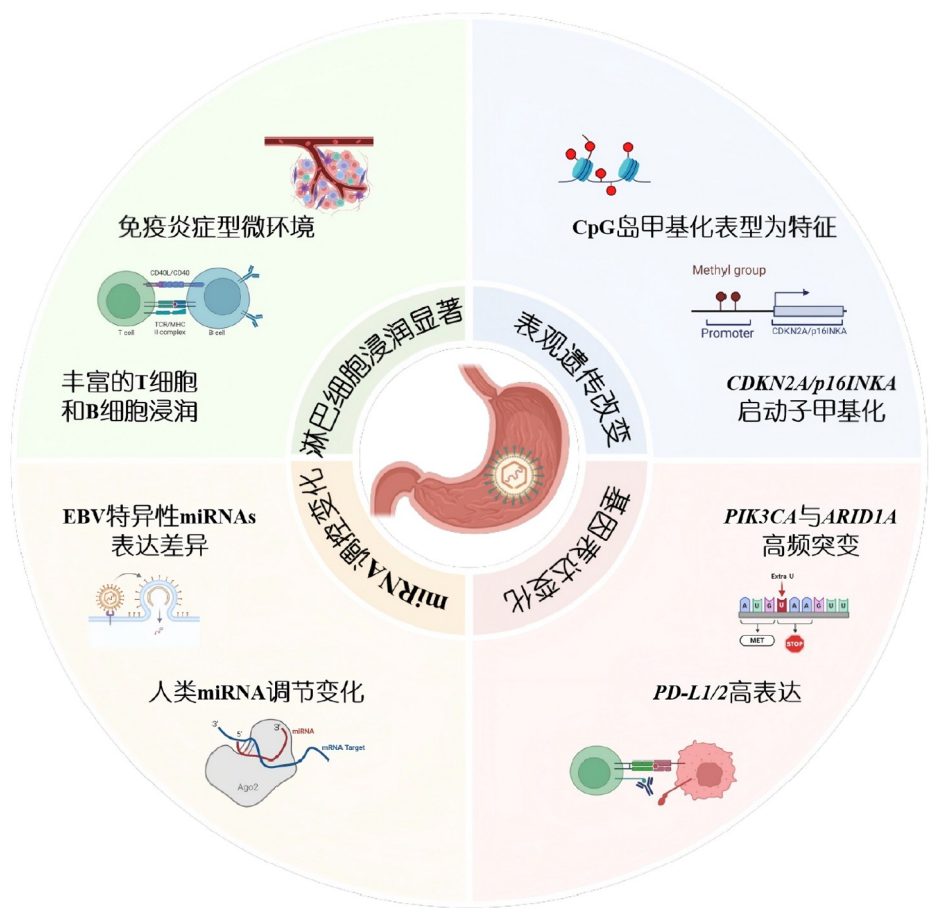


图 1 EBV相关性胃癌的肿瘤微环境特征
Figure 1 Tumor microenvironmental characteristics of EBVaGC

较少^[3]。PIK3CA突变与Akt通路的激活、肿瘤生长和侵袭性密切相关^[22]。除PIK3CA和ARID1A外,参与Wnt和Notch信号通路或细胞周期和染色质调节的基因,比如PTEN, SMAD4, CTNNB1和NOTCH1等,在EBVaGCs中也经常发生突变^[23]。此外,EBVaGC中常伴有染色体9p24.1的扩增,该区域包含编码JAK2, PD-L1和PD-L2的基因^[23,24],导致EBVaGC中PD-L1的高表达^[3,25],有研究指出,EBV感染可通过激活IRF3,从而增加瘤内IFN- γ 水平,进一步提高肿瘤中PD-L1的表达^[26]。

2.3 EBVaGC的表观遗传改变

在EBVaGCs中,除基因层面的变异外,表观遗传层面的失调亦频繁出现。这些失调体现在DNA甲基化模式的改变、EBV特异性miRNAs的表达差异,以及人类miRNAs的调节变化等方面。EBVaGCs经常被归入

高甲基化(CIMP-H)类别^[27,28]。已有研究显示超过1000个基因在EBV的影响下出现甲基化水平的改变,包括Wnt和蛋白激酶信号通路相关的基因^[29-31]。

3 EBV相关性胃癌的治疗与免疫治疗前景

3.1 免疫治疗的应用与效果

EBVaGC的总体治疗原则与其他胃癌患者相同,但其独特的肿瘤免疫微环境使其可能更易从免疫治疗中获益^[32]。2018年,韩国学者采用PD-1抗体治疗了6例EBV阳性的转移性胃癌患者,有效率达到100%^[5]。然而,在随后的多项PD-1抗体单药治疗胃癌的亚组分析中,EBVaGC亚群的有效率仅为16.7%~28.6%^[17,33-35]。在一项前瞻性II期临床研究中,6例EBVaGC患者接受PD-1抗体治疗后未观察到有效病例,研究因此提前中

止^[36]。这些研究表明, EBVaGC是一个异质性群体, 并非所有患者都对PD-1抗体敏感。一项对EBV阳性和阴性胃癌患者单细胞测序的数据分析中发现基线ISG15⁺CD8⁺ T细胞水平可以预测对PD-1抗体的疗效。此外, 研究还发现, 对于PD-1抗体无响应的患者, 其肿瘤浸润的CD8⁺ T细胞中抑制性免疫检查点LAG-3的表达较高, 这提示LAG-3可能是EBVaGC患者潜在的治疗靶点^[21]。此外, 目前也有前瞻性临床研究正在探索PD-1抗体联合CTLA-4抗体在EBV阳性胃癌中的疗效(NCT04202601)。

3.2 基于甲基化的靶向治疗

鉴于EBVaGC具有高甲基化特征, 靶向DNA甲基化的药物(如DNA甲基转移酶抑制剂和组蛋白去乙酰化酶抑制剂)也逐渐受到关注^[37]。目前阿扎胞苷和地西他滨已获准治疗急性髓系白血病和骨髓增生异常综合征^[38], 并有望应用于EBVaGC的治疗。

3.3 预后特征与生存率

在TCGA的4个分子分型中, EBV亚型具有独特的

肿瘤微环境, 初诊时EBVaGC中晚期患者的发生率低, 预后最好^[39], EBVaGC的3年生存率显著高于EBVnGC(分别为76.8%和58.2%)^[17]。

4 未来研究方向与临床应用

EBVaGC是一种特殊亚型的胃癌, 发生率为1.3%~30.9%, 具有独特的生物学特征, 多见于男性患者, 预后较好, 对免疫治疗具有较高的敏感性。未来研究需要进一步揭示EBV如何影响胃癌细胞的生长、分化和转移等生物学过程。基于EBVaGC的免疫微环境特征, 通过研究免疫化疗耐药和敏感性的潜在机制, 识别对治疗有反应的特定免疫细胞亚型, 从而筛选出可能受益的患者群体。对于免疫耐药的患者, 需深入探索耐药机制, 以开发更有效的免疫治疗策略。同时, 有必要开展前瞻性临床试验, 评估新的免疫治疗策略在EBVaGC中的疗效和安全性。通过加强病毒学、肿瘤学、免疫学等多学科的合作与交流, 共同推动EBVaGC的研究进展。

参考文献

- 1 Burke A P, Yen T S, Shekitka K M, et al. Lymphoepithelial carcinoma of the stomach with Epstein-Barr virus demonstrated by polymerase chain reaction. *Mod Pathol*, 1990; 3: 377–380
- 2 Shibata D, Weiss LM. Epstein-Barr virus-associated gastric adenocarcinoma. *Am J Pathol*, 1992, 140: 769–774
- 3 The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*, 2014; 513: 202–209
- 4 Salnikov M Y, MacNeil K M, Mymryk J S. The viral etiology of EBV-associated gastric cancers contributes to their unique pathology, clinical outcomes, treatment responses and immune landscape. *Front Immunol*, 2024, 15: 1358511
- 5 Kim S T, Cristescu R, Bass A J, et al. Comprehensive molecular characterization of clinical responses to PD-1 inhibition in metastatic gastric cancer. *Nat Med*, 2018, 24: 1449–1458
- 6 Song H, Srivastava A, Lee J, et al. Host inflammatory response predicts survival of patients with Epstein-Barr virus-associated gastric carcinoma. *Gastroenterology*, 2010, 139: 84–92.e2
- 7 Luo B, Wang Y, Wang X F, et al. Expression of Epstein-Barr virus genes in EBV-associated gastric carcinomas. *World J Gastroenterol*, 2005, 11: 629–633
- 8 Borozan I, Zapata M, Frappier L, et al. Analysis of Epstein-Barr virus genomes and expression profiles in gastric adenocarcinoma. *J virol*, 2018, 92
- 9 Caldwell R G, Wilson J B, Anderson S J, et al. Epstein-Barr virus LMP2A drives B cell development and survival in the absence of normal B cell receptor signals. *Immunity*, 1998, 9: 405–411
- 10 Gires O, Zimmer-Strobl U, Gonnella R, et al. Latent membrane protein 1 of Epstein-Barr virus mimics a constitutively active receptor molecule. *EMBO J*, 1997, 16: 6131–6140
- 11 Qiu M, He C, Lu S, et al. Prospective observation: clinical utility of plasma Epstein-Barr virus DNA load in EBV-associated gastric carcinoma

- patients. *Intl J Cancer*, 2020, 146: 272–280
- 12 Sarshari B, Ravanshad M, Rabbani A, et al. Quantitative analysis of Epstein-Barr virus DNA in plasma and stomach biopsies of patients with gastric cancer. *Virus Genes*, 2023, 59: 351–358
 - 13 He H C, Han R, Xu B H, et al. Circulating Epstein-Barr virus DNA associated with hepatic impairment and its diagnostic and prognostic role in patients with gastric cancer. *Front Med*, 2022, 9: 1028033
 - 14 Takada K. Epstein-Barr virus and gastric carcinoma. *Mol Pathol*, 2000, 53: 255–261
 - 15 Naseem M, Barzi A, Brezden-Masley C, et al. Outlooks on Epstein-Barr virus associated gastric cancer. *Cancer Treatment Rev*, 2018, 66: 15–22
 - 16 Song H J, Kim K M. Pathology of Epstein-Barr virus-associated gastric carcinoma and its relationship to prognosis. *Gut Liver*, 2011, 5: 143–148
 - 17 Qiu M Z, He C Y, Yang D J, et al. Observational cohort study of clinical outcome in Epstein-Barr virus associated gastric cancer patients. *Ther Adv Med Oncol*, 2020, 12: 1758835920937434
 - 18 Chia N Y, Tan P. Molecular classification of gastric cancer. *Ann Oncol*, 2016, 27: 763–769
 - 19 Panda A, Mehnert J M, Hirshfield K M, et al. Immune activation and benefit from avelumab in EBV-positive gastric cancer. *J Natl Cancer Inst*, 2018, 110: 316–320
 - 20 Zheng X, Wang R, Zhang X, et al. A deep learning model and human-machine fusion for prediction of EBV-associated gastric cancer from histopathology. *Nat Commun*, 2022, 13: 2790
 - 21 Qiu M Z, Wang C, Wu Z, et al. Dynamic single-cell mapping unveils Epstein-Barr virus-imprinted T-cell exhaustion and on-treatment response. *Sig Transduct Target Ther*, 2023, 8: 370
 - 22 Jang S H, Kim K J, Oh M H, et al. Clinicopathological significance of elevated PIK3CA expression in gastric cancer. *J Gastric Cancer*, 2016, 16: 85–92
 - 23 Chen Z H, Yan S M, Chen X X, et al. The genomic architecture of EBV and infected gastric tissue from precursor lesions to carcinoma. *Genome Med*, 2021, 13: 146
 - 24 Morales-Sanchez A, Fuentes-Panana E M. Epstein-Barr virus-associated gastric cancer and potential mechanisms of oncogenesis. *Curr Cancer Drug Targets*, 2017, 17: 534–554
 - 25 Kawazoe A, Kuwata T, Kuboki Y, et al. Clinicopathological features of programmed death ligand 1 expression with tumor-infiltrating lymphocyte, mismatch repair, and Epstein-Barr virus status in a large cohort of gastric cancer patients. *Gastric Cancer*, 2017, 20: 407–415
 - 26 Lima Á, Sousa H, Medeiros R, et al. PD-L1 expression in EBV associated gastric cancer: a systematic review and meta-analysis. *Discov Onc*, 2022, 13: 19
 - 27 Kusano M, Toyota M, Suzuki H, et al. Genetic, epigenetic, and clinicopathologic features of gastric carcinomas with the CpG island methylator phenotype and an association with Epstein-Barr virus. *Cancer*, 2006, 106: 1467–1479
 - 28 Yau T O, Tang C M, Yu J. Epigenetic dysregulation in Epstein-Barr virus-associated gastric carcinoma: disease and treatments. *World J Gastroenterol*, 2014, 20: 6448–6456
 - 29 Zhao J, Liang Q, Cheung K, et al. Genome-wide identification of Epstein-Barr virus-driven promoter methylation profiles of human genes in gastric cancer cells. *Cancer*, 2013, 119: 304–312
 - 30 Zhao Z, Liu W, Liu J, et al. The effect of EBV on WIF1, NLK, and APC gene methylation and expression in gastric carcinoma and nasopharyngeal cancer. *J Med Virol*, 2017, 89: 1844–1851
 - 31 Zhang L, Wang R, Xie Z. The roles of DNA methylation on the promotor of the Epstein-Barr virus (EBV) gene and the genome in patients with EBV-associated diseases. *Appl Microbiol Biotechnol*, 2022, 106: 4413–4426
 - 32 Geng R X, Zheng Z B, Dai X Y, et al. Immune checkpoint inhibitors in solid tumors (in Chinese). *Sci Sin Vitae*, 2021, 51: 1180–1192 [耿瑞璇, 郑志博, 戴晓艳, 等. 免疫检查点抑制剂在实体瘤中的应用. 中国科学: 生命科学, 2021, 51: 1180–1192]
 - 33 Mishima S, Kawazoe A, Nakamura Y, et al. Clinicopathological and molecular features of responders to nivolumab for patients with advanced gastric cancer. *J Immunother Cancer*, 2019, 7: 24
 - 34 Xie T, Liu Y, Zhang Z, et al. Positive status of Epstein-Barr virus as a biomarker for gastric cancer immunotherapy: a prospective observational study. *J Immunother*, 2020, 43: 139–144
 - 35 Wang F, Wei X L, Wang F H, et al. Safety, efficacy and tumor mutational burden as a biomarker of overall survival benefit in chemo-refractory gastric cancer treated with toripalimab, a PD-1 antibody in phase Ib/II clinical trial NCT02915432. *Ann Oncol*, 2019, 30: 1479–1486
 - 36 Sun Y T, Guan W L, Zhao Q, et al. PD-1 antibody camrelizumab for Epstein-Barr virus-positive metastatic gastric cancer: a single-arm, open-

- label, phase 2 trial. *Am J Cancer Res*, 2021, 11: 5006–5015
- 37 Di L J, Zhang J, Zhu W G. Progress in the research of epigenetic regulators in cancer therapy (in Chinese). *Sci Sin Vitae*, 2023, 53: 1546–1563 [邱龙江, 张俊, 朱卫国. 表观遗传调控因子在癌症治疗中的研究进展. *中国科学: 生命科学*, 2023, 53: 1546–1563]
- 38 Kuo H K, Griffith J D, Kreuzer K N. 5-Azacytidine-induced methyltransferase-DNA adducts block DNA replication *In vivo*. *Cancer Res*, 2007, 67: 8248–8254
- 39 Sohn B H, Hwang J E, Jang H J, et al. Clinical significance of four molecular subtypes of gastric cancer identified by the Cancer Genome Atlas Project. *Clin Cancer Res*, 2017, 23: 4441–4449

Epidemiology, molecular characteristics, and clinical application of immunotherapy strategies for EBV-associated gastric cancer

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EBV-associated gastric cancer (EBVaGC) is a type of gastric cancer related to the infection of Epstein-Barr virus (EBV), with a low incidence rate. EBVaGC tends to occur in younger patients, male predominance, and is often diagnosed as locally advanced with a good prognosis. The tumor microenvironment of EBVaGC is characterized by significant lymphocyte infiltration, contributing to a more active immune landscape. Patients with advanced EBVaGC have a higher response rate to immune checkpoint inhibitors compared to patients with ordinary gastric cancer. This article reviews the disease characteristics and the treatment progress of EBVaGC.

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